UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/214,670	06/20/2008	William H. Robinson	STAN-528 (S06-380)	2625

77974 7590 05/25/2017

Stanford University Office of Technology Licensing
Bozicevic, Field & Francis LLP
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
05/25/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte WILLIAM H. ROBINSON,
MICHAEL HOLERS, and KEVIN DEANE[1]

Appeal 2016-003281
Application 12/214,670
Technology Center 1600

Before ULRIKE W. JENKS, JOHN E. SCHNEIDER,
and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to methods of prognosis for the probability of developing rheumatoid arthritis. The claims have been rejected for lack of adequate written description, as indefinite, as claiming non-statutory subject matter, and as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

---

[1] Appellants identify the Real Party in Interest as the Board of Trustees of the Leland Stanford Junior University and the Regents of the University of Colorado. (Br. 1.)

STATEMENT OF THE CASE

The Specification discloses that "[a]utoimmune disease occurs when a specific adaptive immune response is mounted against self antigens. . . . Autoimmunity may be initiated by the activation of antigen-specific T cells, although the specific triggering mechanism remains unknown." (Spec. ¶ 2.) The Specification also discloses that "[r]heumatoid arthritis [RA] may be caused by T_H1 cells specific for antigens present in joints. Engagement with this antigen triggers the T cells to release lymphokines that initiate local inflammation within the joint." (*Id.* at ¶ 3.) According to the Specification, "[r]heumatoid arthritis is a complex disease and also involves antibodies, often including an IgM anti-IgG autoantibody called rheumatoid factor [RF]." (*Id.*)

> Appellants' invention relates to methods
>
> for prognostic classification of individuals into subtypes with respect to development of autoimmune disease, which subtypes are informative of the patient's probability of developing overt autoimmune disease. The patterns of circulating levels of serum autoantibodies and/or cytokines identified herein provides for a signature pattern that can discriminate individuals who have a high probability of developing overt autoimmune disease from those who have a low probability of developing overt autoimmune disease.

(*Id.* at ¶ 9.)

Claims 1, 4–8, and 18–22 are on appeal. Claim 1 is illustrative:

> 1. A method for the prognosis of an individual prior to signs of overt autoimmune disease for the probability of development of overt rheumatoid arthritis, the method comprising:

> determining a cytokine signature pattern for median levels of interleukin 6 (IL-6) from a blood sample obtained from said individual;
>
> determining an autoantibody signature pattern for median levels of at least 3 autoantibody specificities from a sample obtained from said individual;
>
> comparing said cytokine and autoantibody signature patterns with a control signature pattern to generate a determination of prognosis for said individual; wherein a statistically significant match with a positive pattern for an increase in median levels of IL-6 and an increase in median levels of at least 3 autoantibodies for pre-disease subtype or a statistically significant difference from a normal pattern for said increase in median levels of IL-6 and said increase in median levels of at least 3 autoantibodies is indicative that said individual has an increased probability of developing overt rheumatoid arthritis; and providing said individual with said determination of prognosis.

(Br. 22 (Claims App'x).)

The claims stand rejected as follows:

I. Claims 1, 4–8, and 18–22 under 35 U.S.C. § 112, first paragraph (pre-AIA), for failure to comply with the written description requirement.

II. Claim 19 under 35 U.S.C. § 112, second paragraph (pre-AIA), for indefiniteness. (The rejection of claim 7 as indefinite was withdrawn; *see* Ans. 8.)

III. Claims 1, 4–8, and 18–22 under 35 U.S.C. § 101 for claiming patent-ineligible subject matter.

IV. Claims 1, 4, and 6–8 under 35 U.S.C. § 103(a) over Mangialaio[2] and Rantapää-Dahlqvist.[3]

V. Claims 5, 19, and 20 under 35 U.S.C. § 103(a) over Mangialaio, Rantapää-Dahlqvist, Nielen,[4] and Hitchon.[5]

I – WRITTEN DESCRIPTION

"In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue." *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). The disclosure must, nevertheless, convey with reasonable clarity to ordinarily skilled persons that the inventor was in possession of the invention at the time of filing. *See id.*

The Examiner rejected claims 1, 4–8, and 18–22, finding "the specification does not contain a written description of the claimed invention . . . [or] reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed." (Ans. 5.)

---

[2] Mangialaio et al., WO 2006/008183 A1, published Jan. 26, 2006.
[3] Rantapää-Dahlqvist et al., *Antibodies Against Cyclic Citrullinated Peptide and IgA Rheumatoid Factor Predict the Development of Rheumatoid Arthritis*, 48:10 ARTHRITIS & RHEUMATISM 2741–49 (2003).
[4] Nielen et al., *Increased Levels of C-Reactive Protein in Serum From Blood Donors Before the Onset of Rheumatoid Arthritis*, 50:8 ARTHRITIS & RHEUMATISM 2423–27 (2004).
[5] Hitchon et al., *A Distinct Multicytokine Profile Is Associated with Anti-Cyclical Citrullinated Peptide Antibodies in Patients with early Untreated Inflammatory Arthritis*, 31:12 THE JOURNAL OF RHEUMATOLOGY 2336–46 (2004).

The Examiner's position is, in effect, that the Specification and claims as originally filed fail to support determining the levels of the various combinations of cytokines and autoantibodies that are presently recited in the claims. For instance, with respect to claim 4, the Examiner finds "the specification does not provide support for a method of determining medial levels of IL-6, at least three (Previously two) additional cytokines, and at least three autoantibodies." (*Id.*)

We are unpersuaded. As Appellants point out, support for the claims is found throughout the Specification and the original claims. For example, Appellants identify paragraph 131, which describes arrays with "reagents for quantification of at least two, at least three, at least four, at least five or more markers are selected from IP-10 (CXCL-10), MCP-1, CRP, eotaxin, GM-CSF . . . IL-1β, IL-6, and TNF-α," thus disclosing numerous combinations of cytokines. (Br. 6 (citing Spec. ¶ 131).) Appellants identify original claims 1, 2, and 9 as providing support for determining the levels of cytokine (like IL-6) and at least three autoantibodies. (*Id.* at 4 (citing original-dependent claim 9 ("said signature pattern comprises quantitative data for at least 3 autoantibodies.").) Appellants further identify Table 11 and Table 12 of the Specification, which describe various combinations of cytokines and autoantibodies used to test samples. (Br. 7.) This includes, for example, "Anti-CCP and/or any 2 RFs [thus at least 3 autoantibodies] and ≥5 cytokines/chemokines positive." (Spec. 51, Table 11; *see also id.* at Table 10 (identifying IL-6 among various other cytokines).)

The Examiner provides additional grounds for rejecting the claims under § 112, first paragraph. (Ans. 6–7.) More specifically, the Examiner

finds the Specification and original claims fail to provide support for the comparing step "to generate a determination of prognosis for said individual" and the step of "providing said individual with said determination" as recited in claims 1, 18, and 19. (*Id.*) The Examiner further finds the step of "providing a specific therapeutic agent to treat said individual" as recited in claim 7 lacks written description support. (*Id.*)

These additional grounds are also unpersuasive. As Appellants note, the comparing step to generate a determination of prognosis is supported by at least paragraphs 98 and 100 of the Specification. (Br. 8; Spec. ¶¶ 98, 100.)[6] The Specification expressly discloses that "[t]he resulting information [i.e., a prognosis] may be transmitted to a patient or health professional." (Spec. ¶ 120.) And, after describing numerous therapeutic agents (*see id.* at ¶¶ 73–96), the Specification discloses "biomarkers may identify patients likely to respond to specific therapeutic agents, and could thereby be used to guide selection of the most appropriate agent(s) to treat individual patients" (*id.* at ¶ 97).

In short, Appellants' disclosure, while broad in many respects, is not lacking adequate written description as asserted by the Examiner. Based on the preponderance of the evidence, we are unpersuaded the skilled person would not recognize possession of (i) the various combinations of cytokines and autoantibodies for use in Appellants' claimed method of prognosis, or

---

[6] Certain cites in Appellants' Brief to paragraphs of the Specification appear to be one number off. For example, Appellants' Brief cites to paragraphs 97 and 99 (Br. 8), but the applicable paragraphs appear to be paragraphs 98 and 100. Reference to the Specification in this Decision refers to the version filed on June 6, 2008.

(ii) the steps of comparing to generate a prognosis, providing an individual with the prognosis, or providing a therapeutic agent to treat the individual. We, thus, reverse the rejections under § 112, first paragraph.

II – INDEFINITENESS

The Examiner finds the term "classification" in claim 19 is vague, undefined in the Specification, and thus indefinite. (Ans. 4, 11.)

Appellants disagree, citing paragraphs 9 and 11 in the Summary of the Invention portion of the Specification. Paragraph 9 discloses, in relevant part, that "methods are provided for *prognostic classification* of individuals into *subtypes* with respect to development of autoimmune disease, which *subtypes are informative of the patient's probability of developing overt autoimmune disease*." (Spec. ¶ 9 (emphasis added).) Paragraph 11 provides numerous examples of potential classifications: "with regard to pre-disease states, one can classify individuals as: normal (N); RF+ anti-CCP- and pre-disease (RFPD); RF+ anti-CCP- not pre-disease (RFNPD); anti-CCP+ RF- pre-disease (CCPRFNPD) . . . and overt RA (RA)." (Spec. ¶ 11.) The Specification provides further examples of sub-classifications of overt RA (e.g., "very early disease (< 6 months of symptoms)"). (*Id.*; *see also id.* at ¶ 116 ("Classification of interest include, without limitation, the assignment of a sample to one or more of the autoimmune disease states: i) autoimmune state vs. non-autoimmune state, (ii) pre-disease vs. normal, (iii) progression to severe vs. mild disease . . . .").)

Appellants have the better position. The term "classification" may be broad, but we are unpersuaded it would not be reasonably understood by skilled persons when read in light of the Specification. *In re Miller*, 441

F.2d 689, 693 (CCPA 1971) ("[B]readth is not to be equated with indefiniteness.") The Examiner has not met the burden to establish that claim 19 is indefinite. *In re Packard*, 751 F.3d 1307, 1311 (Fed. Cir. 2014).

III – SUBJECT MATTER ELIGIBILITY

Claim 1

In analyzing patent eligibility under 35 U.S.C. § 101, the Supreme Court has set forth a "framework for distinguishing patents that claim [patent-ineligible] laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S.Ct. 2347, 2355 (2014). According to that framework, first "we determine whether the claims at issue are directed to one of those patent-ineligible concepts." *Id.* "If so, we then ask, '[w]hat else is there in the claims before us?'" *Id.* (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S.Ct. 1289, 1297 (2012).) To answer this second question,

> we consider the elements of each claim both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent-eligible application. [The Supreme Court has] described step two of this analysis as a search for an inventive concept — *i.e.*, an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.

Id. (internal citations and quotation marks omitted).

With the exception of claim 7, addressed separately below, Appellants argue the patentability of the claims rejected under § 101 as a group. We select claim 1 as representative. 37 C.F.R. § 41.37(c)(1)(iv).

The Examiner finds that the invention of claim 1 is drawn to patent-ineligible subject matter. (Final Act. 8; Ans. 7, 11–14.) More specifically, the Examiner finds "the methods of the instant claims, determining increased cytokine and autoantibody levels as a predictor of RA, recite a judicial exception." (Final Act. 8.) According to the Examiner, "[t]he steps simply describe the judicial exception, i.e., the natural relationship between certain biological markers and the possible development of rheumatoid arthritis." (*Id.*) And, with respect to the claimed steps individually and in combination, the Examiner finds they "are no more than nominally or insignificantly related to the judicial exception" and "are conventional and routine within the art." (*Id.*) For example, the Examiner finds that "determining of cytokine or autoantibody levels, are routinely used by others." (*Id.*)

We agree with and adopt the Examiner's findings of fact, reasoning, and conclusion that claim 1 is ineligible for patenting under 35 U.S.C. § 101. (Final Act. 8; Ans. 7, 11–14.) Claim 1 is directed to a law of nature or natural principle — the correlation between levels of cytokines and autoantibodies in an individual's blood sample and the likelihood of that individual developing rheumatoid arthritis. As Appellants' Specification confirms, the invention is, in effect, simply making a prognosis of rheumatoid arthritis based on this natural correlation. (Spec. ¶¶ 9–14.)

Turning to step 2 of the *Alice/Mayo* framework, the claim as a whole, considering the elements individually and as an ordered combination do not impart a sufficient inventive concept. As noted by the Examiner, "the natural correlation of elevated protein marker and autoantibody levels in RA patients is the *only* allegedly novel concept set forth in the specification and

claims." (Ans. 13.) Indeed, Appellants expressly acknowledge that the claimed steps relating to determining signature patterns for median levels of cytokines and autoantibodies involve well-known and conventional assaying steps known to skilled persons. (*See*, *e.g.*, Spec. ¶ 98 ("A variety of different assays can be utilized to quantitate the presence of cytokines. Many such methods are known to one of skill in the art, including ELISA, fluorescence immunoassays, protein arrays, [etc.]"); *see also id.* at ¶ 113; Deane Decl. 4 ("the rheumatoid factor and anti-CCP2 assays are considered 'standard' because they are commercially available")[7].)

The claimed step reciting "comparing said cytokine and autoantibody signature patterns with a control signature pattern to generate a determination of prognosis" itself encompasses an abstract mental process. It is also not materially different than routine steps employed by those skilled in the art, where cytokine and autoantibody levels in a patient sample are compared against a healthy control. (*See*, *e.g.*, Mangialaio 12:13–17 ("increased amounts of the at least two biomarkers and optionally of RF in the sample from the subject relative to the amounts . . . in a control sample . . . indicates that the subject has or is likely to develop RA").) *See Mayo*, 132 S.Ct. at 1298 ("well-understood, routine, conventional activity previously engaged in by scientists who work in the field . . . is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law."); *see also Parker v. Flook*, 437 U.S. 584, 590 (1978) ("The notion that post-solution activity, no matter how conventional

---

[7] *See* the Declaration of co-inventor Kevin Deane, M.D., Ph.D., dated November 4, 2014 ("Deane Decl.").

or obvious in itself, can transform an unpatentable principle into a patentable process exalts form over substance.")

The step of "providing said individual with said determination of prognosis" also fails to impart a sufficient inventive concept. This is nothing more than a generic instruction to apply the natural law — informing the patient of the prognosis based on the patent-ineligible natural correlation. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015), *cert. denied* 136 S.Ct. 2511 (2016) ("'simply appending conventional steps, specified at a high level of generality,' [is] not enough to supply an inventive concept.") (quoting *Mayo*, 132 S.Ct. at 1300); *Mayo*, 132 S.Ct. at 1294 ("one must do more than simply state the law of nature while adding the words 'apply it.'") (citation omitted).

In short, the claim limitations individually and in combination are insufficient to transform the patent-ineligible natural law into patent-eligible subject matter.

We address Appellants' arguments below:

Appellants contend "others can still apply and use the natural principle in other methods" for example by "using less than the recited subset of markers or using alternative markers." (Br. 12; *see also id.* at 14 ("others may detect expression of autoantibodies using a method that does not require a blood sample".) In other words, Appellants contend that claim 1 does not preempt all practical applications of the natural principle.

Appellants' suggestion that complete preemption of all practical applications of the law of nature is required to sustain a rejection under § 101 is unpersuasive. The extent of preemption is a consideration, but the

absence of complete preemption is not dispositive. On this point, the Federal Circuit's analysis in *Ariosa* is instructive. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015), *cert. denied* 136 S.Ct. 2511 (2016). In *Ariosa*, the patent owner argued "the particular application of the natural phenomena that the [] patent claims embody are narrow and specific" and, thus, did not "preclude alternative methods [of using cffDNA] in the same field." (*Id.* at 1378.) The Federal Circuit rejected that argument and held that "[w]hile preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." (*Id.* at 1379.)[8] And, according to the Federal Circuit, "[w]here a patent's claims are deemed only to disclose patent ineligible subject matter under the *Mayo* framework, . . . preemption concerns are fully addressed and made moot." (*Id.*)[9]

---

[8] *See also Ultramercial Inc. v. Hulu LLC*, 722 F.3d 1335, 1346 (Fed. Cir. 2013) ("the Supreme Court has stated that, even if a claim does not wholly pre-empt an abstract idea, it still will not be limited meaningfully if it contains only insignificant or token pre- or post-solution activity—such as identifying a relevant audience, a category of use, field of use, or technological environment.") (citations omitted), *vacated and remanded, Wildtangent, Inv. v. Ultramercial LLC*, 134 S.Ct. 2870 (2014) (remanding for consideration in light of *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S.Ct. 2347 (2014)).

[9] *See also Flook*, 437 U.S. at 589–90 (rejecting patent applicant's argument that "[h]e does not seek to wholly preempt the mathematical formula, since there are uses of his formula outside the petrochemical and oil-refining industries that remain in the public domain."). Updated Patent Office guidance related to subject-matter eligibility also recognizes that "the courts do not use preemption as a stand-alone test for eligibility" and instructs that "while a preemptive claim may be ineligible, the absence of complete preemption does not guarantee that a claim is eligible." (*See* July 2015

Appellants' argument fares no better than the similar, but rejected, argument in *Ariosa*. Here, as in *Ariosa*, Appellants' "attempt to limit the breadth of the claims by showing alternative uses of [the law of nature] outside of the scope of the claims does not change the conclusion that the claims are directed to patent ineligible subject matter." *Ariosa*, 788 F.3d at 1379. For claim 1, Appellants determine the levels of IL-6 and at least three autoantibodies. But we are unpersuaded this makes claim 1 patentable under Section 101. As discussed above in the Section I, related to the written description rejection, the Specification discloses numerous potential combinations of cytokines and autoantibodies that are assayed through routine techniques. Given this broad disclosure, even if claim 1 did not foreclose certain combinations of cytokines and autoantibodies at present, the draftsperson may pursue these combinations through future claims, thus expanding the preemptive reach of Appellants' invention drawn to the natural law.[10] *Cf. In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 764 n. 4 (Fed. Cir. 2014) ("The preemptive nature of the claims is not ameliorated even if we accept Myriad's argument that other methods of comparison exist. If the combination of certain routine steps were patent eligible, so too would different combinations of other routine steps.")

Update on Subject Matter Eligibility, 80 Fed. Reg. 45429 at 8 (July 30, 2015) (footnotes and citations omitted).)

[10] Although claim 1 recites "a blood sample," the Specification discloses that tissue samples can derive from numerous sources such as synovial fluid, saliva, milk, urine, and several others. (Spec. ¶ 102.)

Appellants argue "the elements [of claim 1] relate to the natural principle in a significant way" and it "is clearly an important and practical application of the alleged natural correlation." (Br. 12–13.) But even important and useful discoveries may fail to satisfy § 101. *See*, *e.g.*, *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S.Ct. 2107, 2117 (2013) ("[Myriad] found an important and useful gene . . . [but] [g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry.") The method claimed in *Mayo*, for example, was useful for determining the efficacy or toxicity of certain drug dosages, yet the Court held the method was unpatentable because it merely informed the relevant audience about certain laws of nature with additional steps that consisted of conventional activity. *Mayo*, 132 S.Ct. at 1295, 1298.[11] The same is true here. As described above, claim 1 merely appends generic, routine, and conventional steps that are little more than an instruction to apply a natural correlation and make a prognosis about rheumatoid arthritis.

Appellants argue "a step of assaying expression levels requires a transformation of a biological molecule . . . into a detectable signal (e.g., a fluorescent signal[,] which is detectable by a man-made instrument, e.g., a PCR machine[])]." (Br. 13.) As an initial matter, claim 1 does not recite any particular assay or machine required in the process. To the contrary, it merely recites "determining a cytokine signature pattern for median levels" of IL-6 and autoantibodies. The Court in *Mayo* also rejected a position

---

[11] *Cf. Mayo*, 132 S.Ct. at 1305 ("We need not determine here whether, from a policy perspective, increased protection for discoveries of diagnostic laws of nature is desirable.")

similar to the one advanced by Appellants. That is, the Court rejected the reasoning that the processes were patent eligible because they involve "transforming the blood by analyzing it to determine metabolite levels." *Mayo*, 132 S.Ct. at 1302–03. In so doing, the Court held that, while the "machine or transformation" test provides a clue to patentability, it does not trump the law-of-nature exclusion. *Id.* at 1303. Here, to the extent there is any alleged transformation of a biological molecule (e.g., a biomarker in a blood sample), it involves only an obvious and routine step that applies the natural law. This fails to transform claim 1 into eligible subject matter. *Id.* at 1299 ("Post-solution activity that is purely conventional or obvious . . . cannot transform an unpatentable principle into a patentable process.") (internal quotation marks and alterations omitted).

Inasmuch as Appellants address the § 101 rejection based on the 2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena and/or Natural Products ("the 2014 Guidance") (Br. 10–14), the 2014 Guidance is encompassed by analysis under the *Alice/Mayo* framework. And, for the reasons discussed above, Appellants' arguments concerning the patentability of claim 1 under the 2014 Guidance are unpersuasive.

Claim 7

Claim 7 depends from claim 1 and adds the step of "providing a specific therapeutic agent to treat said individual if prognosed with an increased probability of developing rheumatoid arthritis." (Br. 22.)

Appellants argue claim 7 satisfies § 101 because it includes a treatment step. In support, Appellants cite *Classen Immunotherapies v.*

Biogen IDEC, 659 F.3d 1057 (Fed. Cir. 2011) and a portion of "Examiner training slides." (Br. 14.)

Appellants' argument is unpersuasive. *Classen* was decided before *Alice* and *Mayo* and, in view of these later and controlling precedents, does not support the notion that reciting a treatment step in a claim drawn to a natural law necessarily transforms the claim into patent-eligible subject matter. We are not persuaded that appending a generic, routine, and obvious post-solution treatment step — as recited in Appellants' claim 7 — provides a sufficient inventive concept to satisfy § 101. *See also Mayo*, 132 S.Ct. at 1297 (holding the claimed "'wherein' clauses simply tell a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient.")

As to the "Examiner training slides" cited by Appellants, these slides are not the law. In addition, in the very same slide cited by Appellants, it provides an example of a claim that does recite a law of nature: "Identifying a disease using a naturally occurring relationship between the presence of a substance in the body and incidence of disease."[12] This resembles Appellants' claims, which are drawn to the natural correlation between cytokine and autoantibody levels in a blood sample, and the incidence or prognosis of developing rheumatoid arthritis. Appellants have simply added a generic step of treating the individual with a therapeutic agent. No new or

---

[12] (*See* Evaluating Subject Matter Eligibility Under 35 U.S.C. § 101: March 2014 Update at slide 21 (slides dated March 19, 2014 available at https://www.uspto.gov/patents/law/exam/myriad-mayo_slides_20140319.pdf) (last visited May 12, 2017).

unconventional agent or medical procedure is actually recited. Accordingly, claim 7 fails to recite patent-eligible subject matter under § 101.

For the reasons above, we conclude the Examiner established by a preponderance of the evidence that claims 1 and 7 are patent ineligible under 35 U.S.C. § 101. Claims 4–6, 8, and 18–22 have not been argued separately and fall with claim 1.

IV & V – OBVIOUSNESS

Claims 1, 4, and 6–8 Over Mangialaio and Rantapää-Dahlqvist

Appellants argue the patentability of the claims as a group and we select claim 1 as representative.

The Examiner finds that Mangialaio "teaches a method for the prognosis of the development of rheumatoid arthritis." (Ans. 2.) More specifically, the Examiner finds that Mangialaio teaches "determining if said [individual] has significantly increased levels of the cytokines TNF-α, MCP-1, IL-6, and/or IL-1β, in combination with increased levels of RF (an autoantibody)." (*Id.* (citing Mangialaio 12).)

The Examiner finds Mangialaio "differs from the claimed method only in that it does not teach the employing of an autoantibody pattern of at least three autoantibodies." (*Id.* at 2–3.) The Examiner thus turns to Rantapää-Dahlqvist and finds it "teach[es] that the autoantibodies anti-CCP, IgG-RF, IgM-RF, and IgA-RF are all found at significantly elevated levels in pre-RA patients." (*Id.* at 3 (citing Rantapää-Dahlqvist Table 1).)

The Examiner concludes it would have been obvious "to perform the prognosis method of [Mangialaio] including a profile of anti-CCP, IgG-RF, IgM-RF, and IgA-RF autoantibodies in addition to the profile of the

cytokines . . . taught by the primary reference." (*Id.* at 3.) The Examiner reasons that the skilled person would have predictably modified the prior art in this way "to perform a more specific and accurate method of prognosing the development of RA." (*Id.*)

We adopt the Examiner's fact finding, reasoning, and conclusion that claim 1 would have been obvious over Mangialaio and Rantapää-Dahlqvist. (Ans. 2–3, 14–17.) We address Appellants' arguments below.

Appellants contend Mangialaio "fails to provide a disclosure that enables prognosis of disease prior to onset of clinical symptoms, and fails to teach a combination of multiplex cytokine and multiplex autoantibody specificities for such a purpose." (Br. 16.)

We are unpersuaded. As the Examiner correctly points out, Mangialaio teaches "a method for determining whether a subject has *or is likely to develop* rheumatoid arthritis." (Mangialaio 12:8–9 (emphasis added); Ans. 14.) Mangialaio does so by assaying levels of at least two biomarkers (e.g., various cytokines, including IL-6) and RF (an autoantibody) in a patient sample and comparing against a control sample from a healthy individual. (*Id.* at 12:13–20.)[13]

Although Mangialaio does not expressly teach determining the amounts of multiple autoantibodies (apparently preferring IgM-RF (*see id.* at 15:18–19)), that teaching is supplied by Rantapää-Dahlqvist. (Rantapää-Dahlqvist 2741 ("Anti-CCP antibody and RFs of all isotypes predated the

---

[13] Mangialaio teaches "[m]iniaturized and multiplexed immunoassays may also used to screen a biological sample for the presence or absence of proteins such as antibodies." (Mangialaio 11:8–9.)

onset of RA by several years. . . . The specificity for RA can be further increased by combining the presence of anti-CCP antibody with the presence of rheumatoid factor.") Table 1 of Rantapää-Dahlqvist shows the prevalence of anti-CCP antibodies and IgG, IgM, and IgA RFs in dozens of RA "pre-patients" meaning those "whose blood samples were obtained before the onset of any RA symptoms." (*Id.* at Table 1.) Rantapää-Dahlqvist further teaches "[c]ombining anti-CCP antibodies with any RF isotype increased the specificity, reaching 100% in some analyses (Table 2)." (*Id.* at 2745.)

Absent persuasive argument or evidence to the contrary, it would have been obvious to combine the teachings of Mangialaio and Rantapää-Dahlqvist, both of which relate to biomarkers indicating a likelihood of developing rheumatoid arthritis. Appellants do not persuasively rebut the Examiner's reasoning that assaying for additional biomarkers, known for their association with RA, would have been obvious and would have been expected to produce more specific and accurate prognoses. (Ans. 3.)

Appellants, citing declaratory evidence, then argue that using "multiple autoantibodies as well as cytokines and chemokines can be used to predict the timing of onset of future RA." (Br. 17.) For example, Appellants contend certain combinations "could be used to predict 'imminent' RA as defined as onset of RA within 2 years." (*Id.* at 18.) Notably, claim 1 is not so narrow and, instead, recites a more general prognostic method (e.g., "said individual has an increased probability of developing overt rheumatoid arthritis.") *See also In re Self,* 671 F.2d 1344, 1348 (CCPA 1982) ("[A]ppellant's arguments fail from the outset because . . . they are not based on limitations appearing in the claims."). In any

event, the preponderance of the evidence persuades us that combining Mangialaio and Rantapää-Dahlqvist in the manner proposed by the Examiner would predictably allow for a prognosis of the likelihood of developing RA. Indeed, that is precisely what the references suggest. (*See*, *e.g.*, Mangialaio 12:9–29; Rantapää-Dahlqvist 2741, 2746 (Table 2).)

Appellants contend "results disclosed in the present application provide for an unexpected benefit." (Br. 18; Deane Decl. 3.) As noted by the Examiner, however, "[i]t is unclear if the Inventor intends to actually claim unexpected results." (Ans. 16.) Appellants submitted no Reply Brief to clarify that, in fact, secondary considerations comprising unexpected results are being alleged. That being said, with respect to the results Appellants are identifying (Br. 18–20; Deane Decl. 4–8), Appellants have not shown that such results are commensurate in scope with claim 1 or reflect more than a difference in degree that would have been expected based on the combination of known RA-associated biomarkers. *In re Lindner*, 457 F.2d 506, 508 (CCPA 1972) ("It is well established that the objective evidence of nonobviousness must be commensurate in scope with the claims."); *In re Skoner*, 517 F.2d 947, 950 (CCPA 1975) ("Expected beneficial results are evidence of obviousness of a claimed invention."). In short, assaying for multiple cytokines and RA-related autoantibodies may "lead[] to improved diagnostic accuracy for established disease" as asserted by Appellants (Br. 20), but we are unpersuaded that provides sufficient evidence of nonobviousness that outweighs the evidence of obviousness.

The preponderance of the evidence supports the Examiner's conclusion that claim 1 would have been obvious over Mangialaio and

Rantapää-Dahlqvist. Claims 4 and 6–8 were not argued separately and fall with claim 1.

Claims 5, 19, and 20 Over Mangialaio, Rantapää-Dahlqvist, Nielen, and Hitchon

We adopt the Examiner's findings of fact, reasoning, and conclusion of obviousness with respect to claims 5, 19, and 20. (Ans. 2–4; 14–18.)

Appellants provide no separate substantive argument in support of the patentability of claims 5, 19, or 20. Appellants assert that "a combined profile is significantly more powerful than the sum of its parts" and "[w]hile any individual marker may have a small predictive ability, the power to genuinely make a prognosis requires analysis of a complex pattern." (Br. 21.) These general assertions fail to show error in the Examiner's determination of obviousness for the reasons explained above.

SUMMARY

We reverse the rejection of claims 1, 4–8, and 18–22 under 35 U.S.C. § 112, first paragraph, for failure to satisfy the written description requirement.

We reverse the rejection of claim 19 under 35 U.S.C. § 112, second paragraph, for indefiniteness.

We affirm the rejection of claims 1, 4–8, and 18–22 under 35 U.S.C. § 101 for claiming patent-ineligible subject matter.

We affirm the rejection of claims 1, 4, and 6–8 under 35 U.S.C. § 103(a) over Mangialaio and Rantapää-Dahlqvist.

We affirm the rejection of claims 5, 19, and 20 under 35 U.S.C. § 103(a) over Mangialaio, Rantapää-Dahlqvist, Nielen, and Hitchon.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED